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Non-regulated water contaminants: emerging research

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Abstract

Those chemical pollutants that are regulated under various international, federal, and state programs represent but a small fraction of the universe of chemicals that occur in the environment as a result of both natural processes and human influence. Although the number of these targeted chemicals might be minuscule compared with the universe of both known and yet-to-be identified chemicals, an implicit assumption is that these selective lists of chemicals are responsible for the most significant share of risk with respect to environmental or economic impairment or to human health. This paper examines some of the less-discussed aspects of the background and assumptions that underlie society's relationship with chemical pollutants in water, particularly with respect to the need for a more holistic understanding of exposure and risk.

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1. Introduction

The major intent of this synopsis is to open some windows onto the landscape of published resources for pursuing the many and disparate aspects of “emerging” research regarding water pollutants; the approach used in this

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paper is unorthodox in that a decision was made to enhance accessibility to the literature by providing references to Web pages containing direct links to a wide expanse of work. One particularly diverse spectrum of water pollutants—pharmaceuticals and personal care products (PPCPs)—is used to illustrate some of the many points discussed regarding “emerging” pollutants. A broad array of research needs and gaps has been compiled for PPCPs (Daughton, 2004a, comp. 2004a); in general, these needs and gaps are equally pertinent to many other water pollutants.

Briefly summarized are some of the many, disparate issues that require consideration in assessing the challenges in ensuring public health and ecological integrity with regard to the use of water. The sections that follow are pertinent to answering questions such as: What types of “new” chemical stressors and sources can be anticipated in water? How important are these stressors in the context of human health? What research gaps might hamper the safeguarding of public health? What disconnects might exist between policy and science?

1.1. Pollution and “emerging” science

Several different dimensions can account for the universe of potential chemical toxicants. From each of these dimensions comes a different perspective in terms of how the continuum of the chemical universe “pie” is sliced. Previously unrecognized, unexpected, or unanticipated scenarios for exposure to chemicals can be viewed from a number of different perspectives. Discussions regarding “emerging” pollutants often get confused because of the failure to define (i) what is meant by “emerging” and (ii) the dimension of the chemical universe around which the discussion is focused. The dimensions include chemical classes (according to chemical functionality; chemicals of totally new structure), type of use (new uses in either the industrial or consumer realms), type of effect (newly discovered but prior-existing effects or totally new receptor targets or ligand–receptor interactions), mechanism of action, source (new types of sources or previously unknown origins for existing chemicals), and exposure route (pathways that had not been anticipated or previously discounted as not possible) (Daughton, 2001a). Each dimension can intersect with the others to various degrees. These different perspectives often inject confusion into discussions oriented to anticipating future risks or uncovering existing, but previously unrecognized, risks. For example, discussions regarding endocrine disrupting compounds (EDCs) are sometimes equated with discussions concerning PPCPs. But the former is defined according to type of biological effect or mechanism of action, while the latter is defined by chemical classes and types of use; and the two intersect only to a limited extent (some PPCPs are EDCs and vice versa). Some of the many issues associated with “emerging” science and pollutants have been captured in a discussion centered around PPCPs as pollutants (Daughton, comp. 2004b).

1.2. The universe of chemical pollutants

Countless galaxies of chemical classes have continual presence in waters—regardless of the water's purity. A water's "purity," a concept that breeds much confusion in its own right (Daughton, 2004b), is merely a reflection of the types and concentrations of these chemicals. The number of chemical contaminants at trace levels can exceed those present at higher levels. As the power of analytical chemistry increases, the types of chemicals that can be detected increase, and the limits of concentration at which they can be measured are continually lowered; analytical chemistry plays a key role in expanding and refining our ever-changing perspective of water purity (Daughton, comp. 2004c). These chemicals comprise the broad spectrum of anthropogenic chemicals (those purposefully synthesized and indirectly produced by human activities—drinking water disinfection by-products are one example) as well as "natural products" (those created both by natural physicochemical or biological processes—an example being geosmin, the off-flavor bicyclic alcohol produced by certain algae and fungi). Anthropogenic pollutants gain entry to surface and groundwaters as a result of manufacturing emissions, waste disposal (e.g., incineration, landfills), accidental releases (e.g., spills), purposeful introduction (e.g., pesticides, groundwater recharge, sewage sludge application to land), and consumer activity (which includes both the excretion and purposeful disposal of a wide range of naturally occurring and anthropogenic chemicals such as PPCPs). All of these sources but the last have long been recognized as major potential routes of pollutant release. Consumer activities have only recently been recognized as a potentially major, long-standing source of uncontrolled nonpoint, diffuse pollution.

As of March 2004, nearly 23 million organic and inorganic substances (excluding biosequences such as proteins and nucleotides) had been indexed by the American Chemical Society's Chemical Abstracts Service in their CAS Registry (CAS, 2004a). Roughly one-third of these (over 7 million) were commercially available, representing a 23% increase over the prior 9-month period. In contrast, only about a quarter million (230,000) of these are inventoried or regulated by numerous government bodies worldwide (CAS, 2004b).

While the *known* universe of organic chemicals might seem large, the universe of *potential* organic chemicals (those that could possibly be synthesized and those that already exist but which have not yet been identified) is unimaginably large. To get an idea as to the numbers of distinct organic chemical entities that could hypothetically be synthesized and added to a limitless, ever-expanding known chemical universe, consider the back-of-the-envelope calculations of Bohacek et al. (1996), which yielded over 10^{60} distinct structures that are possible with a total of merely 30 atoms of just C, N, O, or S! Far more than 10^{60} structures would be possible if the wide spectrum of other heteroatoms (including common ones such as P or the halogens) was included, or even larger numbers of C, N, O, and S. Clearly, there are essentially no limits to the types of possible organic

chemicals. The possibilities are only beginning to emerge from the efforts of synthetic organic chemists or combinatorial chemistry.

The high potential for the continued proliferation of new PPCPs (as well as myriads of other anthropogenic chemicals) poses substantial (and perhaps insurmountable) challenges to the evolution and design of viable systems based on a chemical-by-chemical approach for regulating (or monitoring) the occurrence of pollutants in the environment. Just as an example, as of March 2004, more than 140,000 bioactive compounds were in various phases of drug research and development (Prous Science, 2004). The rapid evolution of the “omics” revolution will undoubtedly feed an expansion of new drug entities that has already been underway (Daughton, 2003a). New drug entities, many with mechanisms of action never before encountered by biological systems, can be expected to enjoy continued introduction to commerce—while others are retired or withdrawn from market.

For any sample collected from the environment, a large (but unknown) portion of its organic constituents are not (or cannot) be identified. Toxicity can be associated with constituents from both groups of chemicals—those that can be identified [either through “target” analysis, where the chemicals being analyzed for (known as “analytes”) are preselected, or through nontarget characterization, where no particular chemical is being searched for, such as in forensics], as well as from those that cannot be identified (as a result of limitations in the repertoire of available chemical analysis tools).

Attempts to fully characterize the chemical composition of an environmental sample are rare because they are very demanding of time and resources; historically, they have been attempted most frequently for the easiest environmental “matrix,” ambient air. Such studies attempt to identify and quantify every organic chemical (necessarily limited to those present above detection limits) and seek to achieve a mass balance around total organic carbon. But even after thorough analysis, a portion of the organic carbon will remain unaccounted for (comprising those solutes that cannot be detected for any number of reasons). Significantly, almost always these unidentified compounds comprise an unknown fraction of all those present (unless carbon balances are calculated—a very onerous task), so it is rarely known how significant their presence is. These unidentified chemicals are neglected, ignored, omitted, or overlooked because of any number of limitations or idiosyncrasies of the many tools that compose the repertoire of the analytical chemist (Daughton, comp. 2004c).

1.3. Pollution from personal actions, activities, and behaviors

As an example of chemical pollution from consumer activities (in contrast to the origins for most “conventional” regulated pollutants), the U.S. EPA and other federal agencies such as the USGS in the late 1990s began to examine the occurrence, sources, fate, and potential for environmental and human health effects of pharmaceuticals and personal care products (PPCPs) as

environmental pollutants. These diverse galaxies of chemicals comprise potentially thousands of distinct parent structures, each of which can gain entry to the environment merely by consumer end use (such as excretion and bathing) and by disposal of expired or otherwise unwanted materials to waste drains. The numbers of these chemical entities are then susceptible to amplification simply by the action of biological and physicochemical transformation processes, which can create cascades of other modified structures (such as chains of metabolites), some of which possess biological activity of their own. While PPCPs are considered by many to be “emerging” pollutants, one can safely assume that any consumer chemical has the potential to enter the environment from the first day it is introduced to commerce. In this sense, PPCPs (except for those just introduced to commerce) are not examples of emerging pollutants (that is, those that are just beginning to occur), but rather, it is the *recognition* of their potential significance or environmental ramifications that is actually emerging. In this sense, they are *emerging concerns* rather than emerging pollutants.

The complex aspects of the many issues associated with PPCPs as pollutants are covered in the EPA’s Web site devoted to this topic (Daughton, comp. 2004d). Although PPCPs comprise a very large and diverse spectrum of pollutants, most of which have received little attention, there are possibly numerous others, many of which environmental scientists undoubtedly are not yet even aware. Some examples of more recently recognized pollutants (many of which have origins from multitudes of consumer products) include brominated flame retardants [such as polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD); e.g., see Remberger et al., 2004] and the multiuse perfluoroalkylated synthesis/transformation chemicals such as the fluorotelomer alcohols (FTOHs) and the interrelated perfluoroalkyl sulfonates and carboxylates (e.g., perfluorooctane sulfonate, PFOS, or perfluorooctanoic acid, PFOA; see: Martin et al., 2004); in general, fluorinated chemicals can have enhanced environmental persistence, and their transformation pathways are poorly understood. A special issue of *Environmental Engineering Science* (Sedlak and Alvarez-Cohen, 2003) summarizes what has been revealed regarding a number of unregulated water pollutants, most of which have probably occurred as contaminants in treated wastewaters as well as in the environment for quite some time, but whose presence is only beginning to be widely recognized.

2. Alternative perspectives

Over the last few years, the appellation “emerging” has been applied to pollutants with such increasing frequency that its meaning is becoming diluted. In reality, those pollutants that are truly “emerging” (those that have just gained entry to the environment—for example, because they are new to commerce) are

sometimes confused with those whose presence has just been elucidated but which have long been present.

2.1. “Emerging” pollutants versus emerging concerns

There are a number of different perspectives from which to view the many dimensions of “emerging” (Daughton, comp. 2004b). One example is that of PPCPs (see Daughton, comp. 2004d), which include many substances that have long been present in the environment (but whose presence and significance are only now being elucidated) as well as those entities that are new to commerce. The moniker “emerging” is also sometimes intended not to refer the pollutant itself, but rather to a newly hypothesized concern regarding an old pollutant (pollutants that have long occupied our attention can gain new notoriety with the revelation of new aspects of their occurrence, fate, or effects; acrylamide in cooked foods is one example)—old pollutants, new concerns versus new pollutants, and unknown issues.

2.2. Only but one piece of the pollutant pie

Since the 1970s, the impact of chemical pollution has focused almost exclusively on lists of conventional “priority pollutants,” especially those collectively referred to as “persistent, bioaccumulative toxicants” (PBTs) or “persistent organic pollutants” (POPs). The relatively small number of conventional, regulated pollutants, however, represents but one piece of a much larger universe of potential pollutants—one of largely unknown scope. That biological systems can suffer exposure to countless chemical stressors, only a small number of which are regulated, poses many currently unanswerable questions regarding risk. More perspective and the potential ramifications of this are available (see “The Universe of Organic Chemicals” at Daughton, comp. 2004c; also Daughton, comp. 2004e).

2.3. The exposure-risk puzzle

Those substances historically subject to regulatory oversight represent but a very small subset—largely a historical consequence of expediency and necessity. For example, the current lists of regulated pollutants evolved from those established in the 1970s. A major factor to consider in regulation has necessarily been the availability of suitable off-the-shelf chemical analysis technology (e.g., sufficient selectivity and limits of detection); risk per se was not necessarily the sole factor in listing decisions. Partly for these reasons, the majority of the individual chemicals released to the environment (or xenobiotics created in the environment) are not regulated. Just because these “uncontrolled” pollutants are not regulated, however, does not mean that they do not pose risks. But what portion of overall risk they pose is unknown.

2.4. Persistent, bioaccumulative toxicants

A consensus view had emerged of three commonalities that purportedly dictate the highest propensity for adverse effects from chemical stressors. Such stressors need to: (1) possess structural stability (persistence or long environmental half-lives); (2) be lipophilic and thereby more amenable to passively crossing cellular membranes, resulting in concentration and accumulation in lipids and fat (bioconcentration leading to bioaccumulation via the food chain); and (3) possess acute or chronic toxicity in their own right. While each of these factors is unquestionably significant, less appreciated is that they are not necessarily required for a chemical to be environmentally significant. These three factors deserve further consideration with respect to their restrictiveness in defining risk.

2.4.1. Reassessing “persistence”

One of the hallmarks used to distinguish those environmental pollutants that are the focus of regulatory actions is environmental *persistence*—resistance of chemical structures to alterations by biological or physicochemical transformation. But contrary to this requirement are those unknown numbers of pollutants that are conveyed to receiving waters by sewage treatment plants and whose continual release can give them a “pseudo-persistent” presence in any aquatic environment—regardless of whether they are structurally stable. This alternative view was first formulated with respect to PPCPs (see p. 761 in Daughton, 2003a), many of which have a continual presence (regardless of environmental half-life) in certain aquatic environments simply because their degradation is offset by constant replenishment (analogous to a microbial chemostat).

2.4.2. Reassessing the attributes required for bioavailability and toxicity

Four examples serve to show, at least hypothetically, that in addition to persistence, lipophilicity and acute toxicity are not exclusive attributes for pollutants to pose risk. Chemicals can gain access to intracellular domains by mechanisms that do not rely on the passive diffusion promoted by lipid solubility (the major route by which the fat-soluble pollutants bioconcentrate and eventually bioaccumulate). Properties of certain chemicals and materials can promote indiscriminate, promiscuous intracellular access in the absence of high lipid–water partition coefficients. (1) While most drugs rely on passive transport across the gut wall, some are actively transported. In fact, one of the current strategies under investigation for improved drug delivery is the design of drugs that capitalize on active transport (Daughton, 2003a) via direct ligand-carrier transport or transcytosis (where the ligand binds to a cell-surface receptor which is then transported across the membrane by endocytosis of an induced vesicle). This property could allow such chemicals, as water-soluble pollutants, to bioconcentrate, seemingly in defiance of predictions based on lipophilicity. (2) The small, subcellular scale of nanoparticles can facilitate their promiscuous entry to

intracellular domains (lipid solubility is irrelevant), thereby circumventing cellular defenses. The size and conformation of these materials alone (rather than their actual chemical composition) holds the potential to adversely affect biological systems, such as via surface-mediated effects (e.g., sorption and catalysis) or the ability to evade host defenses by freely penetrating or permeating cellular membranes. Certain nanoparticles have the potential to indiscriminately concentrate within their porosities or on their surfaces a wide spectrum of chemicals and thereby serve as Trojan horses for ferrying their chemical hitchhikers across biological membranes (facilitated transport), irrespective of cellular defensive barriers such as efflux pumps; indeed, this ability is being pursued in the design of more effective approaches to drug delivery. Moreover, simply the sorption of endogenous proteins to nanoparticles within an organism could theoretically elicit an immune response as a result of altering the native conformation of the exposed protein. Discussions regarding the possible environmental ramifications of nanomaterials are just emerging (see links at [CBEN, 2004](#); [Daughton, comp. 2004f](#)). (3) The manufactured nanoparticles used in nanotechnology are an ill-defined class of substances that have extraordinarily large surface-to-size ratios, and, while not necessarily possessing toxicity of their own, they consequently possess high potential for catalyzing reactions involving other chemicals. This single characteristic of the nanoscale imparts nanomaterials with properties that differ dramatically from those of their “macro” counterparts made from the same elemental constituents and poses concerns with regard to unexpected or unforeseen interactions with biological systems. Although the products of these catalyzed reactions can be toxic themselves, damaging free radicals are frequently produced as by-products. Nanoparticles, in this sense, are examples of *indirect* toxicants—where exposure to the parent chemical is not a prerequisite for adverse effects. Another example of an indirect stressor is antibiotics, which can elicit adverse outcomes by way of selecting for pathogen resistance or by altering microbial community structures (see links at [Daughton, comp. 2004g](#)). (4) Almost always forgotten in consideration of acute toxicity is that certain substances can elicit adverse outcomes far after exposure has ceased and thereby escape the formulation of causal connections (also, see Section 2.8.2 regarding *post hoc ergo propter hoc*). Such delayed-onset toxicity is almost never considered in epidemiological studies simply because of the daunting challenge. Irreversible delayed-onset toxicity can manifest itself weeks, months, or years after exposure in the form of carcinogenicity (aflatoxins, asbestos), teratogenicity (e.g., thalidomide), hepatotoxicity (e.g., pyrrolizidine alkaloids), or neurotoxicity (e.g., organophosphorus nerve agents).

2.5. *Inherently biased monitoring data*

The data collected from water monitoring can be biased in two ways—the first resulting from the actual analytical protocol (e.g., analyzing aqueous filtrates and discarding the retentates) and the second a consequence of ignoring large classes

of potential chemical stressors as a result of the exigency to focus on lists of preselected analytes (“target-based” analysis). The use of water monitoring data based on “free” (dissolved) concentrations to predict total environmental loads of a particular pollutant has the potential to yield misleading values that are biased low (perhaps even by orders of magnitude). This is particularly true for those pollutants that reside in alternative physicochemical forms that serve as *hidden reservoirs*, such as excreted metabolic conjugates (which can be reconverted back to their parent forms) and residues tied up as ligands or reversible precipitates or sorbed to suspended particulates or sediments. These considerations are particularly pertinent to antibiotics (Daughton, 2002). With respect to obtaining a holistic view of risk, target-based environmental monitoring necessarily yields a distorted, filtered view of environmental occurrence by purposefully and inadvertently neglecting an unknown (and perhaps substantial) portion of unidentified constituents (see Daughton, comp. 2004h). In the final analysis, consideration should be given to the quip adapted from an Einstein quotation “Not everything that can be measured is worth measuring, and not everything worth measuring is measurable” (Daughton, 2003a).

2.6. *Critical importance of interfaces*

Interfaces and their associated heterogeneous microenvironments at the junctures of dissimilar phases can act as cauldrons for complex interactions and transformation of water pollutants. Interfacial phenomena are insufficiently understood with respect to the removal or storage of xenobiotics as well as the creation of new pollutants. Complex and poorly understood interface processes pose numerous questions. As an example, consider the low levels of dissolved antibiotics in environmental waters. Aqueous dissolved monitored levels, which are usually orders of magnitude below those required to select for antibiotic resistance, may be irrelevant if interface phenomena can serve to bring together much higher concentrations at solid surfaces where biofilms develop. Could microenvironments and niches (such as interfaces occupied by biofilms) serve to maximize exposure concentrations as well as resistance-gene selection and horizontal gene transfer? Upstream sewage trunk lines are one example and biosolids are another where this could occur (Daughton, 2002). The water–air interface, where monomolecular films of lipophilic and amphiphilic pollutants can concentrate, add yet further complexity and a host of other questions.

2.7. *Need for holistic exposure assessments*

The exposure environment to which environmental toxicologists have traditionally focused their attention is limited to the “conventional” pollutants that comprise the various lists of regulated pollutants (see Daughton, comp. 2004c). Many of these are the “high-volume” industrial chemicals (and

manufacturing by-products) and those substances specifically designed to kill pests. It is important to note, however, that these chemicals comprise but a very small portion of the numbers of distinct xenobiotics from the universe to which organisms can and do experience exposure. The chemicals composing these high-profile categories are not representative of the full spectrum of known chemical stressors or the multitudes of transformation products. The multifactorial complexity faced by risk assessment includes the exposure frequency and timing, exposure duration, exposure complexity or “totality” (cumulative and aggregate exposure, synergism, and other multiple-stressor interactions), prior exposure history (the foundation for determining exposure “trajectory”), or other factors including delayed-onset toxicity. Given these limitations, it is important that progress be made toward holistic assessments that account for the wide range of potential environmental pollutants and to pinpoint those pollutant scenarios with highest health-effects potential (Daughton, comp. 2004e).

2.8. Reassessing toxicity—real-world multiple exposure at trace levels

Rarely is any organism exposed to but a single chemical stressor at any time. Emphasis needs to shift to developing a working knowledge of real-world exposure—where organisms continually face mixtures of multiple or multitudes of stressors, the composition of which can continually vary through time in terms of the specific chemical constituents and their concentrations; furthermore, stressors include not just chemicals, but also physical (e.g., thermal), psychological (e.g., fear), and biological (e.g., pathogenic) agents. The chemical sea to which an organism is exposed washes against critical windows of vulnerability (e.g., developmental stages or diurnal physiological phases). Such a multitude of possible interactions poses complex challenges for predicting the *trajectory* of exposure outcomes for an organism. These factors are part of the overall consideration of the “4Ts” of exposure, a shorthand term that captures the complete context of an organism’s cumulative exposure to chemical stressors. The “4Ts” describe “toxicant totality tolerance trajectory” and account for an organism’s complete exposure time line (a trajectory outlined by prior multidimensional exposure history) and the fact that a major objective of all organisms is to maintain homeostasis (in the face of continual perturbation by stressors). Homeostasis can be maintained only within the tolerance bounds for the organism’s regulatory and biochemical defensive repertoire. So the paradigm of the 4Ts sets the stage for the overall true risk as reflected by the sum total of exposure to all toxicants (anthropogenic and naturally occurring) throughout the historical multidimensional space and trajectory of all other exposure variables. A key aspect to this concept is the critical state determined by the 4Ts—that state at which an additional single exposure event can result in an irreversible adverse effect, one that violates homeostasis. A discussion and

cartoon illustration of the 4Ts is available (Daughton, comp. 2004e). A particular class of stressors that greatly complicates risk assessment is those that can elicit delayed-onset toxicity (weeks, months, or years after exposure), the pyrrolizidine alkaloids being an archetypical class.

2.8.1. *Stressor interactions confounding predicted toxicity*

As one of many possible examples of the importance of the 4Ts, the complexity surrounding the many factors involved with exposure, and the unanticipated way in which even vastly dissimilar stressors can interact, consider the greatly enhanced toxicity of the carbamate pesticide, carbaryl, toward amphibians subjected to predatory stress. Carbaryl concentrations from short-term acute exposure that would ordinarily not adversely affect growth or survival can prove lethal when the exposure period is increased and when the exposure occurs in the presence of predatory stress (Relyea, 2003). The end effect is as if the concentration of the chemical stressor was magnified many fold by the increased exposure time and by the nonchemical stressor (a predator cue). A multitude of nonchemical factors can profoundly affect the outcome of exposure to chemical stressors. Rarely are these factors accounted for in conventional ecotoxicity testing protocols.

2.8.2. *Epidemiology and post hoc ergo propter hoc*

A natural consequence of developing a systems-level understanding of exposure and effects would be the minimization of confusing coincidental relationships with actual causes. Correlating exposure (to single chemical stressors) with an observed effect can result in concluding that an exposure causes an effect simply because of a temporal connection—“after this, therefore because of this” (*post hoc ergo propter hoc*). Causality must take into consideration the 4Ts rather than just coincidental connections.

2.9. *Transitioning from chemical-to-chemical regulation to “toxicity apportionment”*

The continual introduction of new chemicals to commerce [many, such as PPCPs, have totally new mechanisms of action (MOAs), most have multiple MOAs, and rarely are the actual MOAs for even the targeted therapeutic effects fully understood] casts doubts as to whether a chemical-by-chemical approach to regulation of water pollutants will continue to be sustainable on a comprehensive scientific footing (Daughton, 2003a; Daughton and Ternes, 1999). With respect to the “exposure universe,” and in a manner analogous to source apportionment, consideration could be devoted toward developing the capability of “toxicity apportionment”—where the objective would be to assign toxicity according to the total numbers and quantities of stressors present, without the need to know their identities in advance. The ideal, ultimate objective would be to close the exposure envelope around all

chemical-exposure constituents—both naturally occurring and anthropogenic. The idea of apportionment is particularly important in accounting for all toxicants that share the same MOA. This alternative approach could consider basing water monitoring programs on assays designed around evolutionarily conserved biochemical features and MOAs rather than on individual chemical entities. Such an MOA-based approach could include assays measuring, for example, inhibition/induction of cellular stress response (e.g., heat shock protein synthesis coupled with the ubiquitin–proteasome pathway), CYP (cytochrome P-450) induction/inhibition, and multidrug transporter activity (efflux pumps, which serve as a critical defensive system for aquatic organisms). This approach could be the best way to automatically account for a multitude of stressors sharing a common MOA (cumulative exposure), stressors newly introduced to commerce, and pollutants not yet identified.

2.10. Growing questions regarding the pervasiveness, significance, and ramifications of low-level effects and hormesis

As the concentrations of chemical residues in treated waters are continually lowered by advances in treatment technology, and as the detectable levels are further reduced by analytical chemists (see Figs. 1–4 at Daughton, comp. 2004c), the toxicological significance of ultralow-dose exposure needs to be better understood. Concern is heightened for those organisms (such as in aquatic environments) that suffer continual, multigenerational exposure to complex mixtures of low-level toxicants. The toxicology of most xenobiotics is poorly understood at low levels. As one example of the seemingly paradoxical, unexpected effects that can occur, the same degree of analgesia achieved by a conventional therapeutic dose of morphine can be achieved by a dose 6 orders of magnitude lower when co-administered with an ultralow dose of an opioid receptor antagonist (Daughton, 2003a).

Particularly needed is to elucidate the significance of low-level effects in the range where so-called “paradoxical” dose responses are prevalent [e.g., at levels of nM–pM (μg – ng/L) and below, where the U- or J-shaped nature of dose response curves becomes evident]. An example is hormesis (e.g., see BELLE, 2004), a dose-response phenomenon where noninhibitory effects occur below previously established levels of “no-observed effects.” Despite hormesis being proposed as a justification for permitting low-dose exposures (e.g., because one of its common outcomes is growth stimulation), it is important to remember that (i) any effect (regardless of its anthropocentric interpretation) that perturbs homeostasis has the potential to ultimately result in an adverse outcome and (ii) real-life exposures are to multiple stressors, some of which can share the same MOA, thereby effectively having a combined concentration higher than the hormetic level for a single stressor in isolation from all others.

3. Peeking at the future

While it is not possible to predict the future regarding the many dimensions of chemical pollution, one can hypothesize new paradigms that could develop from now-emerging industries or practices.

3.1. Possible future sources of water pollutants

Two examples are totally new pollutants, never before encountered by biological systems (such as pharmaceuticals with new MOAs and synthetic nanomaterials; see [CBEN, 2004](#)), and totally new sources for substances that never had a significant presence in the environment [such as the transgenic production of proteinaceous therapeutics by genetically altered plants, also known as plant-made pharmaceuticals (PMPs) from “molecular farming” or “biopharming”; see links at [Daughton, comp. 2004i](#)]. With regard to new sources, continued advancements in combinatorial chemistry, coupled with less-costly and more sophisticated robotics, could expand the user-base for the mass synthesis of untold numbers of chemicals for myriads of possible uses. The disposal and escape to the environment of these chemicals from multitudes of dispersed point sources holds the potential for a significant new source of pollutants.

3.2. Develop the means to evaluate and monitor undefinable pollutants—SUDUX

Nanomaterials comprise particles with diameters ranging roughly from 1 nm (10 Angstroms, about the size of 10 hydrogen atoms) to 100 nm. Naturally occurring and certain anthropogenic nanoparticles have long posed toxicological concerns; examples include the inhalation of soot from the pyrolysis or combustion of fuels or even from cooking. Indeed, nanoparticles have been used since antiquity for various purposes, such as in artwork (where the color of certain particles can be dictated solely by controlling their size). The emergence of specially designed and manufactured nanomaterials (which by definition would be “manufactured” from the “bottom-up,” atom by atom) via a multitude of industries could contribute greatly to the load and distribution of nanoparticles in the environment ([CBEN, 2004](#); [Daughton, comp. 2004f](#)). In contrast to “conventional” pollutants, the properties of these materials are dictated more by their molecular or particle size and shape than by their chemical structures or compositions, many of which can be expected to be ill-defined and varied in terms of both composition and conformation.

A host of currently unanswerable questions quickly arise regarding the environmental chemistry and environmental toxicology of these newly created xenobiotics, which could quickly achieve worldwide distribution via widespread use in consumer products. Natural weathering/aging or environmental transformation of nanomaterials from consumer items could hold the potential for creating nearly universal, continual, inadvertent exposure to a large

spectrum of additional ill-defined materials (via respiratory, dermal, and ingestion routes). Many currently unforeseeable environmental and human health ramifications could be posed by reinventing the material world. Both the parent nanoparticles and their associated transformation products can be referred to as structurally undefinable ubiquitous xenobiotics (SUDUX) (Daughton, 2003b). Inherent to the ill-defined structural nature of SUDUX may be its propensity to thwart our chemical analysis wherewithal to monitor environmental occurrence or to measure exposure; currently, these types of potential pollutants can be analyzed only with sophisticated approaches such as single-particle mass spectrometry.

3.3. Inadequate and decaying water infrastructure

Conventional municipal sewage treatment facilities were never designed to remove exotic anthropogenic chemicals with structures and mechanisms of biological action that are foreign to biological degradative/transformation systems. Indeed, the ubiquitous, albeit low level, presence of PPCPs in treated sewage effluent reflects this limitation. Even if existing waste treatment and water treatment facilities together with the associated conveyance distribution networks functioned according to original specifications, the types and quantities of xenobiotics in treated water could continue to rise, partly as a result of the introduction of new chemicals to the marketplace and partly because the nation's water infrastructure requires considerable investment for repair and upgrading (see p. 761 in Daughton, 2003a). An additional infrastructure need is to reduce the occurrence of unpermitted straight-piping, septic systems, and privies, which serve to maximize the release of xenobiotics to the environment (to both surface waters and groundwaters).

3.4. Groundwater recharge

The diminishing quantity and quality of potable source waters are pressures serving to heighten interest in reusing water. Just as with the historic practice of treating domestic wastewaters for discharge to surface waters (which, after sufficient spatial and temporal disconnect, is eventually recycled for drinking), the long-practiced purposeful recharge of groundwater (both indirect and direct) is a major route to achieving water reuse. But the ever-shortening spatial and temporal hydraulic connectivity between the point of wastewater discharge and the point of use for drinking (what Asano calls “increasingly smaller recycle loops”) will pose serious challenges for ensuring human safety and for framing how risk is perceived by the consumer. These challenges will be magnified as the levels of micropollutant residues are reduced and as new pollutants continually emerge. The many issues surrounding society's relationship with groundwater recharge and water reuse have been discussed by Daughton (2004b).

3.5. *Decentralized water re-use*

The growing shortage of freshwater could drive a transition from centralized municipal water treatment and distribution to truly distributed water reuse—where wastewater is both treated and reused at its origin—on site (the ultimate extension of so-called “toilet-to-tap” programs). Such distributed water reuse systems pose unique challenges regarding public acceptance and effective communication of risk (see Sections 3.9 and 3.10). But they also offer advantages regarding independence and the inherent design advantage of ultimate security from large-scale sabotage. Another advantage of recycling water generated directly from the point of original use (as opposed to collective water from domestic, municipal, and industrial generators) is that the universe of microcontaminants that need to be removed is vastly reduced (Daughton, 2004b).

3.6. *Pollution prevention—role of the individual in sustainability*

Depending on the source or the end-use exposure for each “class” of anthropogenic xenobiotics in water supplies, their overall environmental loads could be reduced by instituting any of seemingly unlimited means of pollution prevention strategies. Long practiced at the manufacturing level, pollution prevention has only begun to be implemented or contemplated at the many stages leading up to and including consumer consumption or end use. Successfully engaging the public is critical for making meaningful progress toward sustainability. The extreme diversity of actions that can be designed or implemented to reduce the introduction of PPCPs to the environment serves as but one example for minimizing consumer chemicals as pollutants. Extensive information regarding this example is available at the U.S. EPA’s *PPCPs* Web site (Daughton, comp. 2004j), which is based on the two-part *Green Pharmacy* monograph (Daughton, 2003a,c). Of the many approaches for reducing the introduction of drugs to the environment are consumer-level “take-back” programs (see p. 780 at Daughton, 2003c). While several countries have implemented these programs, the U.S. (at the state level) is only beginning to consider such an approach. As an example, the State of Maine has been particularly proactive in this regard, with a proposal to implement an innovative “mail-back” program (State of Maine Legislature, 2004).

3.7. *Early warning*

An ultimate objective of any program focused on “emerging pollutants” should be to create a mechanism for identifying new environmental pollutants as early as possible—well before their becoming pervasive in the environment. A mechanism for the real-time detection of the presence of new pollutants in water is important not just for protecting the environment and public health from the effects of inadvertent pollution. It would also serve double duty in protecting water

supplies from chemical sabotage (a concern for Homeland Security, see Section 3.7.1). The sheer numbers of potential new contaminants would clearly pose insurmountable obstacles for conventional target-based monitoring approaches. A straightforward way to sidestep this limitation would be to design an early-warning system around the simple approach of detecting “change”—where any perturbation in a water’s normal chemical “fingerprint” (distribution pattern of types and quantities of solutes) would trigger an immediate in-depth chemical analysis to determine the cause (identify the chemicals responsible for the change). Such a nationwide *change-detection* approach was proposed in 2001 (see section “One Proposal for a Nationwide Approach to Identifying Emerging, Nascent Risks: ‘Pollutant Fingerprint Anomalies’” at [Daughton, comp. 2004b](#)). The timely elucidation of newly emerging (or previously unrecognized) pollutants is also critical to uncovering trends in geographic pollutant distribution, prevalence, and loads. Having available long-term change-detection data could greatly assist epidemiological studies, especially those involving cancer clusters, which have long been a bane of toxicologists. Another approach is to leverage the involvement of amateur observers to report unusual phenomena in nature that are possibly the result of chemical stressors; one such proposal was noted by the [Royal Commission on Environmental Pollution \(2003\)](#).

3.7.1. Monitoring-systems for early warning of emerging pollutants automatically affords protection against chemical sabotage

Sabotage of water supplies currently presents a major unaddressed problem with respect to Homeland Security. Traditional target-based monitoring schemes applied to detecting chemical sabotage (monitoring based on predefined lists of potential sabotage agents) could easily be circumvented simply with the use of chemical agents that are not included on such predefined lists. Furthermore, the use of sabotage agents having mechanisms of action that yield symptoms only after delayed periods of time (delayed-onset of action) can easily circumvent any real-time detection device based on the more inclusive (but still not universal) monitoring approaches using biological assays. In contrast, early-warning systems based on chemical-fingerprint “change-detection” (see Section 3.7 above) could prove essential for protecting water supplies.

3.8. Use of pollutants as indicators or surrogates for other types of water pollution

Certain pollutants can be used as tools (probes or tracers) for providing ready indication of the presence of other types of pollutants that are more difficult, costly, or time consuming to measure directly. For example, PPCPs can be used as sentinels of sewage intrusion (to trace sewage plumes or determine the source of groundwater contamination) ([Daughton, comp. 2004k](#)). Monitoring for select PPCPs could also be used for heightening community or societal awareness of adverse behavior (e.g., providing objective measures of community-wide illicit

drug usage; Daughton, 2001b) or of the connection between personal activities and the environment.

3.9. Changing consumer behavior and how risk is perceived (outreach programs and education)

The quality of source waters depends in part on the diffuse impacts of the collective actions, activities, and behaviors of multitudes of individuals—from each of whom minuscule (and seemingly insignificant) contributions combine to yield detectable levels of certain pollutants that otherwise have little origin from industrial activities. Scientists need to better leverage opportunities for providing the public a greater understanding for how its actions are immediately, intimately, and inseparably linked to the environment. The fact that PPCPs occur as environmental pollutants (with still poorly understood ramifications) can be used as an excellent teaching tool (Daughton, comp. 2004l). Societies worldwide are depending increasingly on rapid and complex advances in science and technology. With this in mind, arguments have long been made that optimal, rational, sociopolitical decisions cannot be made without a widespread public grounding in how science works: “It is suicidal to create a society dependent on science and technology in which hardly anybody knows anything about science and technology” (attributed to Carl Sagan). Effective communication of science is also critically important to ensure the continued support of science by the public and to ensure that science plays its due role in the development of policy and the broader social agenda. The importance of science communication and the responsibilities incumbent on scientists is a widely discussed topic (Daughton, comp. 2004m). One example shows how water science could be used to objectify the long-ongoing and emotional society-wide debate regarding the prevalence of illicit drug use—where monitoring for illicit drugs in municipal sewage could be used to form objective, science-based estimates of community-wide collective consumption of illicit drugs, rather than relying on subjective measures derived from inaccurate, biased personal surveys (Daughton, 2001b).

3.10. Communicating risk

A major factor that limits the advancement of science and technology is public acceptance, which is largely driven by the perception of risk and the way in which it is communicated by scientists (Daughton, 2004b, comp. 2004m). Effective risk communication will prove particularly important with regard to the future of water resources for two reasons. First, the numbers of water pollutants newly introduced and newly discovered will continue to expand. Second, as freshwater supplies diminish, the pressure to recycle water will continue to grow. The ultimate culmination of water recycling will

probably be the so-called “toilet-to-tap” programs (eventually those that rely on on-site treatment/recycling) for turning wastewater (e.g., sewage) into drinking water. The occurrence of even minute traces of drugs in certain drinking waters (Daughton, comp. 2004n) can foster the formation of negative mental images for the consumer (regardless of the water’s overall purity), being that the origin of these drugs often derives solely from human excretion. It could prove critical that the public understand the ramifications of these programs (Daughton, 2004b). It might also prove useful that more resources be devoted to studying and improving the communication of risk to the general public. A better understanding is needed of the origins of the chasm existing between hazard/risk communication and how the public perceives risk. This will prove especially important with the growing need to recycle water for drinking, as maintenance of public trust in water supplies will prove critical to sustainable societies—the erosion of public trust in government and industry increases public resistance to adopting change. Regardless of the thoroughness and soundness of the science that will continue to be developed, it might all be for naught without integrating the cognitive sciences (e.g., psychology) into the environmental sciences to develop a better communications interface between science and the public. Public education is particularly important for minimizing the incidence of the so-called “nocebo” response (Daughton, 2004b; see links at Daughton, comp. 2004o), which could possibly play a larger role in the chasm separating hazard assessment and risk perception than previously realized. The nocebo effect (the opposite of the placebo effect) is a real, physiologically adverse outcome caused simply by the suggestion or belief that something (such as a chemical) is harmful, regardless of any inherent toxicity. The nocebo effect could play a key role in the development of adverse health consequences from exposure even to trace levels of contaminants—simply by the power of suggestion.

3.11. Avoiding the “wow-to-yuck trajectory”

Early peeks at advances offered by technology traditionally capture our imaginations. Hypothetical future advances often amplify our anticipation to the point where the future cannot come soon enough. Dr. Kristen Kulinowski (Rice University) coined the term “wow index” to describe this phenomenon (in discussions concerning the evolution of nanotechnology). In certain instances, however, when the public is not properly informed of the potential ramifications of emerging technologies or insufficiently involved in considerations of its adoption, early anticipation can melt away to anxiety or fear. Dr. Kulinowski refers to this as the “wow-to-yuck trajectory.” The widespread public resistance to genetically modified food crops, after an “advertising” period that touted countless benefits, is one example of wow quickly transforming to yuck. It is important that those involved with the “selling” of water recycling to the public learn from this pitfall.

3.12. “Futuring” and the precautionary principle

The traditional way of addressing emerging pollutants or long-recognized pollutants that “resurface” (with new concerns), regardless of how timely, is at best a reactive approach. The fact that corrective reactions are required long after chemicals achieve commercial footholds leads to discussions of the controversies surrounding the *Precautionary Principle* (see links at [Daughton, comp. 2004p](#)). Clearly, a new paradigm would be welcomed—a proactive approach where future concerns are anticipated, long before any preventive or remediation measures would have major economic ramifications. To minimize the emergence of unanticipated concerns, more resources need to be invested in forward thinking, truly anticipatory research programs. These fall under the concept of “futuring”. Futuring should involve the formulation of challenging questions regarding adverse scenarios. Using nanomaterials as one hypothetical example ([CBEN, 2004](#); [Daughton, comp. 2004f](#)), what is the potential for nanomaterial-generated pollutants to create exponentially more xenobiotics, an unknown portion of which may be new to organisms, and would the potential exist for a form of self-perpetuating pollution with forever-changing composition?

3.13. “Literature forensics”—making use of what we should already know—moving from reductionism to holism

An essential component to a productive “futuring” capability is the efficient mining of the vast repositories of often underutilized existing data or knowledge. Often lost in the rapid advances of science and the exponentially growing fruits of its increasingly specialized published literature is the need for higher-level synthesis that transcends the boundaries that are continually pushed to more distant horizons by the need for interdisciplinary applications. This capability is also critical for moving away from science’s entrenched reductionist thinking toward holistic, systems-level understandings. Furthermore, untold useful knowledge remains hidden in works already published. This “knowledge” simply awaits rediscovery. Immeasurable value of the science literature resides in its use to reveal what is knowable. A complex garden of knowledge, the literature is designed to be continually cultivated, grown, harvested, digested, and seeded. In the absence of care, its fruits wither and rot. Neglected and ignored, its vast facts lay strewn about—otherwise capable of revealing much—but in the end, telling nothing. The way in which the literature is used to solve current mysteries is called *literature forensics*. This important topic is covered in depth at [Daughton \(comp. 2004q\)](#).

4. Conclusion

The ideas presented in this paper (partly derived from a series of papers and presentation available at [Daughton, comp. 2004d](#)) are intended to foster a more

pervasive discussion for establishing a holistic view of xenobiotic exposure (e.g., see Daughton, comp. 2004e), with more emphasis placed on nonregulated pollutants. The ultimate technical objective would be to establish the overall significance of chemical stressors (in contrast to nonchemical stressors) for both human health and ecological integrity. The ultimate, unmet challenge is to convey the significance of chemical exposure to the public in a way that allows sound decision making (Daughton, 2004b).

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